Spreading Ischemia After Aneurysmal Subarachnoid Hemorrhage

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Abstract Spreading depolarization (SD) is a wave of mass neuronal and glial depolarization associated with net influx of cations and water. Prolonged SDs facilitate neuronal death. SD induces tone alterations in cerebral resistance arterioles, leading to either transient hyperperfusion (physiological neurovascular coupling) in healthy tissue or hypoperfusion (inverse neurovascular coupling = spreading ischemia) in tissue at risk for progressive damage. Spreading ischemia has been shown experimentally in an animal model replicating the conditions present following aneurysmal subarachnoid hemorrhage (aSAH), in animal models of the ischemic core and penumbra following middle cerebral artery occlusion, and in patients with aSAH. In animals, spreading ischemia produced widespread cortical necrosis. In patients, spreading ischemia occurred in temporal correlation with ischemic lesion development early and late after aSAH. We briefly review important features of SD and spreading ischemia following aSAH.

Keywords Aneurysmal subarachnoid hemorrhage • Spreading depression • Delayed cerebral ischemia

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Introduction

Spreading depolarization (SD) is the generic term for depolarization waves in the central nervous system characterized by abrupt, near-complete sustained depolarization of neurons, observed as a large change of the slow electrical field potential. Moreover, SD is characterized by (1) near-complete breakdown of the transcellular ion gradients [23, 41], (2) extreme shunt of neuronal membrane resistance [3], (3) electrical activity loss (spreading depression) [26], and (4) neuron swelling with dendritic spine distortion [40]. Thus, the term SD describes a near-complete short circuit between neurons and extracellular space electrically, and a cytotoxic edema biochemically and morphologically [23, 40].

Synchronous near-complete sustained depolarization of thousands or millions of neurons with similar spatial orientation produces a large change of the slow extracellular potential as a direct electrocorticographic (ECoG) summary measure

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for SD [3]. In addition to the duration of the slow potential change, pattern and duration of the depression of spontaneous brain electrical activity and the polarity of ultraslow potential components can be assessed in the ECoG to determine the biological significance of a given SD [31].

SD is termed terminal SD in regions where neurons do not repolarize [15]. Terminal SD is always observed in response to heavily noxious situations, such as severe persistent hypoxia, severe focal ischemia (less than about 15 ml/100 g/min) or cardiac arrest. However, strictly speaking, only the initial segment of terminal SD represents the SD process, while the later ultraslow negative potential is assumed to reflect mechanisms of injury and death [31]. In contrast to heavily noxious conditions, mild ischemia induces a cluster of recurrent SDs with intermediate durations as observed experimentally using the endothelin-1 (ET-1) model of mild focal ischemia [8, 9, 31]. Very mild ischemia seems to trigger single, short-lasting events [30] whose patterns are almost identical to those recorded in normally perfused tissue around an ischemic zone where tissue recovers from SD within 1 or 2 min [29]. If oxygen, glucose, and regional cerebral blood flow (rCBF) show tissue gradients, a gradual transition in space from terminal to short-lasting SD via intermediate SD patterns is measured when the depolarization wave travels along those gradients.

While terminal SD is always associated with neuronal death [34], neurons survive short-lasting SD [29, 30]. SDs of intermediate duration are typically observed in the ischemic penumbra after middle cerebral artery occlusion, defined as a region of constrained blood supply in which membrane ion homeostasis is preserved [20]. In those studies, SD occurrence and cumulative duration were correlated with infarct size and dynamics of infarct expansion [4, 18, 27]. Moreover, SDs that were chemically triggered outside the penumbra and that invaded it caused stepwise enlargement of the necrotic core [8, 40]. This suggested that SDs of intermediate duration initiate cascades leading to cell death similar to terminal SDs.

SD presumably entails triggers that activate intracellular signals causing neuronal death. However, this requires a certain minimum duration of a single SD or possibly cumulative duration of multiple SDs. The commitment point has been defined as the time point after onset of SD at which neurons undergoing SD start to be irreversibly damaged [36]. Of note, the neuronal network may transiently recover from such a deleteriously prolonged SD, and cell death may only occur in a delayed fashion. Potential mechanisms by which long-lasting SDs recruit tissue into cell death include the intracellular calcium overload, mitochondrial depolarization, and excessive release of glutamate [6, 33].

Using ECoG, SDs have been shown in abundance in patients with aneurismal subarachnoid hemorrhage (aSAH) and delayed ischemic stroke after aSAH [11, 13], malignant hemispheric stroke [5], spontaneous intracerebral hemorrhage, and traumatic brain injury (TBI) [14, 19, 38]. The full spectrum of SD from short-lasting to very long-lasting events was recorded in patients with aSAH [31] and TBI [19]. Interestingly, SDs also occurred in abundance in patients with delayed cerebral ischemia after aSAH in whom angiographic vasospasm was prevented by nicardipine prolonged-release implants [42]. There is increasing evidence that SDs represent an independent risk factor for poor outcome in patients with TBI [17] and aSAH [12].

The Normal Neurovascular Response to SD

In the normal neurovascular response to physiological neuronal activation and deactivation, neurotransmitter and neuropeptide release during synaptic transmission is involved [1]. Neuronal activation is associated with glutamate-evoked calcium influx in postsynaptic neurons, which activates production of nitric oxide (NO) and arachidonic acid metabolites. This results in vasodilation that reflects both presynaptic activity and the degree of postsynaptic depolarization. Furthermore, astrocytes sense glutamatergic transmission via metabotropic glutamate receptors, and signal vascular smooth muscle via end feet through arachidonic acid pathways [22]. SD is associated with more pronounced changes than physiological neuronal activation, but principles underlying the neurovascular response to SD may be remarkably similar to those underlying the neurovascular response to physiological neuronal activation [6]. This applies to the release of glutamate and vasoeffectors like NO and arachidonic acid metabolites, ion flux directions, and increase in metabolism and energy demand [25, 41].

Thus, rCBF increases in response to SD by more than 100%. This increase in rCBF typically propagates in the tissue together with the depolarization wave [28]. Therefore, it is termed *spreading hyperemia*. The spreading hyperemia seems to serve several purposes, including increased delivery of energy substrates such as glucose and oxygen to the tissue and increased clearance of metabolites from the extracellular space [39]. It outlasts SD and only ends after about 2 min. After the spreading hyperemia, rCBF shows a mild decrease for up to 2 h. This normal mild rCBF reduction after SD is called spreading oligemia [24]. During spreading oligemia, vascular responses to arterial pCO_2 changes and functional activation are attenuated [32].

The Inverse Neurovascular Response to SD

The inverse neurovascular response to SD is a marked, prolonged hypoperfusion due to severe arteriolar constriction that is evoked by SD under specific pathological conditions [6]. The inverse response occurs when there is local dysfunction of the microvasculature. With the inverse response, severe microarterial spasm instead of vasodilation is coupled to the

neuronal depolarization phase of SD [10, 35, 37]. The resulting spreading perfusion deficit prolongs the neuronal depolarization phase since there is no energy for neuronal repolarization. This is observed as a prolonged negative slow potential change, also referred to as a negative direct current (DC) shift. During the inverse neurovascular response, neurons are particularly challenged as energy demand is increased and energy delivery is simultaneously decreased. The resulting prolonged depolarization is therefore more likely to cause lasting neuronal damage, as explained previously. In other words, the inverse neurovascular response to SD can convert a relatively harmless short-lasting SD into a harmful intermediate or even terminal SD. The inverse neurovascular response can thus cause widespread cortical necrosis in animals [7] in contrast to SD under physiological conditions to which hyperemia is coupled [29].

The hypoperfusion as a consequence of the inverse rCBF response to SD is often called spreading ischemia [10] to distinguish it from the harmless physiological spreading oligemia that occurs following SD-induced hyperemia under physiological conditions. Current experimental findings suggest that spreading ischemia results from a vicious cycle due to disturbed microvascular reactivity. This vicious cycle has been explained in more detail elsewhere [6]. Most important, the classic condition that causes this vicious cycle is a decrease of cortical NO availability combined with an increase of baseline extracellular potassium. Both conditions occur when blood lyses in the subarachnoid space after aSAH. Therefore, based on animal experiments, it was suggested that spreading ischemia may be a pathophysiological mechanism involved in the development of delayed cerebral ischemia after aSAH [10].

Spreading Ischemia in Patients After aSAH

Based on this experimental hypothesis, a prospective, multicenter study of the Co-Operative Studies on Brain Injury Depolarizations (COSBID) group was performed [11]. In this study, 13 patients with aSAH were investigated using subdural optoelectrode technology for simultaneous laser-Doppler flowmetry and DC-ECoG, combined with recordings of tissue partial pressure of oxygen. In total, 603 SDs were recorded in 2,467 h of ECoG recording time. SDs were characterized by a DC shift of −10.8 (−9,7, −13,7) mV (median, first, and third quartile, respectively) and a propagation velocity of 2.1 (1.8, 2.9) mm/min. Simultaneous ECoG and rCBF were measured in 1,953 h of recording time, during which 417 SDs were recorded. Isolated SDs were seen in 12 patients. Physiological, absent, or inverse rCBF responses were coupled to such isolated SDs. The normal hyperemic neurovascular response was associated with tissue hyperoxia, whereas tissue hypoxia accompanied the inverse response. In association with structural brain damage, temporal clusters of prolonged SDs were measured in five patients. These clusters were typically associated with the inverse neurovascular response, spreading ischemia. Spreading ischemia could last for over 2 h during such clusters. Progressively hypoxic responses during clusters of SDs were also found in a subsequent study by Bosche and colleagues [2].

Pooling of all SDs with simultaneous recordings of ECoG and rCBF showed that 295 (71%) of 417 SDs had no initial hypoperfusion longer than 0.5 min, 78 (19%) SDs had an initial hypoperfusion of 0.5–2 min, and 16 (4%) had initial hypoperfusions of 2–5 min. The remaining 28 (7%) SDs showed spreading ischemia of 5–144 min in at least one optoelectrode pair. Importantly, the duration of SD-induced hypoperfusion correlated strongly with the duration of depolarization measured by the negative DC shift. These studies therefore suggested that, as in experimental animals, inverse coupling/spreading ischemia is a mechanism in the human brain that converts relatively harmless, short-lasting into deleterious long-lasting SDs.

Low-Frequency Vascular Fluctuations

Combined ECoG and rCBF monitoring also uncovered a characteristic vascular signature that might be used for noninvasive detection of SDs [6]. Low-frequency vascular fluctuations with a frequency of less than 0.1 Hz are determined by the resting spontaneous activity of the normal brain and can be detected by imaging methods such as near-infrared spectroscopy or functional magnetic resonance imaging [16]. SD causes a depolarization block of action potential generation, which disrupts this resting state and results in a spreading wave of depressed spontaneous activity [21]. Using subdural optoelectrode technology for simultaneous laser-Doppler flowmetry and ECoG, it was found that the SD-induced spreading depression of activity was accompanied by a spreading suppression of low-frequency vascular fluctuations in aSAH patients [11]. This characteristic vascular signature was associated with all neurovascular responses to SD, including physiological, absent, or inverse coupling. Importantly, the duration of the suppression of the low-frequency vascular fluctuation correlated significantly ($R = 0.91$) with the duration of suppression of spontaneous ECoG activity.

Conclusion

Because the duration of suppression of spontaneous ECoG activity also correlates with the duration of the negative DC shift during SD, the spreading suppression of low-frequency vascular fluctuations may serve as a novel functional index of SDs and a noninvasive, real-time measure of ischemic cell damage in the human brain.

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